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10/591,321	08/31/2006	Morten Reeslev	36731-000093/US	9441
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HARNESS, DICKEY & PIERCE, P.L.C. P.O. BOX 8910 RESTON, VA 20195			EXAMINER MARTIN, PAUL C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/591,321	Applicant(s) REESLEV ET AL.	
	Examiner PAUL C. MARTIN	Art Unit 1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 15-18, 20-45 and 48-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13, 15-18, 20-45 and 48-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>1/25/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-13, 15-18, 20-45 and 48-51 are pending in this application and were examined on their merits.

The Finality of the last Office Action mailed 04/13/09 is hereby withdrawn in view of the New Rejections herein.

The rejection of Claims 1-4, 6, 7, 10-13, 16, 17, 20, 22-28, 35, 36 and 40-45 under 35 U.S.C. § 102(b) as being anticipated by Tuompo *et al.* (US 5,714,343) has been withdrawn due to the Applicant's amendments to the Claims filed 07/10/09.

The rejection of Claims 1, 3, 4, 6, 7, 10, 11, 14, 15, 17, 20, 22-25, 27, 28, 31, 32, 33, 35 and 36 under 35 U.S.C. § 102(b) as being anticipated by Laine *et al.* (US 6,090,573) has been withdrawn due to the Applicant's amendments to the Claims filed 07/10/09.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Filtration method for detecting Microbial Contamination.

Claim Objections

Claim 18 is newly objected to because of the following informalities: The term "methyumbelliferol" in line 4 of the claim is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3, 7, 9, 15 and 18 are newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claims 3, 7, 9, 15 and 18, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 35 is newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 35 requires that the interaction between the substrates and the contaminants be terminated on the filter or not be terminated. It is unclear how this claim further limits Claim 1 as either ending the reaction or letting it proceed are the only two possibilities for any chemical/biological reaction.

Claim 41 is newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 41 requires that the contaminants be subjected to a signal-enhancing influence. It is unclear what the metes and bounds of a "signal-enhancing influence" would be as the term encompasses anything from temperatures, pH, chemical compounds such as polymethoxy silane, antibiotics, nutrients, etc.

Claim 45 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "and/or" renders the claim indefinite as one of ordinary skill in the art would be able to ascertain what method steps are included or excluded from the method. Claim 45 in line 3 also requires subjecting a medium to a selective substance for yeast, fungi or bacteria.

It is unclear what the metes and bounds of a "selective substance" would be as the term encompasses anything from buffers at certain pH, antibiotics, the presence or lack of specific nutrients or nutrient combinations, etc.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-7, 10-13, 16, 17, 20, 22-30, 35, 36, 40-45 and 48-51 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Tuompo *et al.* (US 5,714,343).

Tuompo *et al.* teaches a method for the detection of viable microorganisms (bacteria), the method comprising a) passing a known volume of liquid medium through a filter from influent side to effluent side in a closed, sterile filter device (Fig. 1) thereby concentrating and retaining microorganisms (bacteria) present on the filter device influent side, b) contacting the influent side of the filter with a liquid vehicle (test solution) containing an enzyme substrate that through contact with constitutively expressed microbial dehydrogenase will produce a detectable moiety,

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and c) allowing the chromogenic substrate to interact with the microorganisms (bacteria) for a period of time wherein the interaction is not terminated and detecting the colored product retained on the filter and correlating the detection of the colored product to the presence of bacteria in the sample (Column 8, Claim 1 and Column 9, Claims 1,2, 4, 5 and 7 and Column 4, Lines 66-67 and Column 5, Lines 1-25).

Tuompo *et al.* teaches wherein prior to step a) the medium is pre-filtered (Column 3, Lines 35-52), wherein the viscosity is reduced by means of dilution prior to step a) (Column 4, Lines 66-67), wherein the filter has a pore size from 0.75 to about 1.2 μm (Column 2, Lines 45-47), wherein several different known volumes of medium containing different amounts of bacteria were passed through a filter in step a) (Column 5, Table 1), wherein detection is performed in a microtiter plate (Column 5, Lines 5-7), wherein the bacteria are subjected to a selective pH incubation (signal enhancing substance) prior to step a) (Column 5, Table 1) and wherein the water soluble substrate MTT which is not retained on the fiber can be used for spectrophotometric methods of detection (Column 3, Lines 22-23).

Tuompo *et al.* teaches that the method can be used on liquid samples from the wood and pulp industry, the sugar industry or urban waste water (Column 2, Lines 30-33).

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It is inherent in the method of Tuompo *et al.* that the liquid vehicle containing the chromogenic substrates comprises multiple substrates providing signals that are combined into one measured signal value because the liquid vehicle contains multiple molecules of the chromogenic substrate MTT which combine to give a total, measurable color formation, and that the amount of substrate does not limit the rate of production of the detectable moiety. It is inherent that the detectable moiety would be detected in the liquid vehicle as some liquid vehicle would inevitably be retained in the filter along with the substrate and colored product. It is further inherent that the rate of production of the detectable moiety would be a function of the quantity of bacteria in the medium as it logically follows that more bacteria would equal more available enzyme for reaction with the substrate and result in a greater rate of production over a sample containing less bacteria (the velocity of an enzyme catalyzed reaction is first order in enzyme concentration). It is an inherent property of the filter device of Tuompo *et al.* would be disposable as nearly everything can be considered "disposable", giving the term its broadest, reasonable interpretation and only depends on the materials used.

The teachings of Tuompo *et al.* were discussed above.

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Tuompo *et al.* did not teach a method wherein the liquid sample was environmental water, wherein the closed, sterile filter device integrates the filter and filter housing into one irreversibly closed structural unit wherein longest cross-sectional axis of the closed, sterile filter device does not exceed a length of 10cm, or wherein the detectable moiety is detectable in an amount of at most 100 picomoles, 50 picomoles, 20 picomoles, 10 picomoles or 1 picomole.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Tuompo *et al.* for the detection of viable microorganisms (bacteria) in liquid samples to detect microorganisms in environmental water samples wherein the detectable moiety cleaved by enzymes characteristic for contaminating microorganisms is in picomolar amounts because Tuompo *et al.* teaches that the method is applicable to many varied liquid samples from biological fluids to industrial or waste water liquids as well as other liquid samples in which the presence of microorganisms is of interest and because it is desirable to detect contamination using the smallest amount of detectable moiety possible. One of ordinary skill in the art would have been motivated to make this modification because the reference clearly teaches its suitability in assaying a wide range of liquid samples.

Further, one of ordinary skill in the art would have recognized the advantageous property of detecting a contaminating microbe in the least amount possible, as obviously detecting a small amount of contamination is better than only detecting gross contamination. One of ordinary skill in the art at the time of the invention would have recognized that the result-effective adjustment of conventional working parameters (e.g., determining the least amount of detectable substrate released by microbial action) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. While the reference does not teach the integration of the filter and filter housing into one irreversibly closed structural unit, wherein longest cross-sectional axis of the closed, sterile filter device does not exceed a length of 10cm, those of ordinary skill in the art would have recognized that making the structure irreversibly closed and of a certain cross-sectional length are merely artisanal design modifications dependent upon personal preference and do not materially change the way the device functions.

There would have been a reasonable expectation in making these modifications because the reference clearly teaches the applicability of the method to assaying any liquid water samples suspected of containing microorganisms and because personal design choices of the devices used in biological methods and detecting miniscule amounts of fluorescent compounds are well known to those of ordinary skill in the art.

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Claims 1-7, 10-13, 16, 17, 20, 22-30, 35, 36, 37, 38, 40-45 and 48-51 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Tuompo *et al.* (US 5,714,343) in view of Koumura *et al.* (US 4,591,554).

The teachings of Tuompo *et al.* were discussed above.

Tuompo *et al.* does not teach a method wherein the substrate that produces a detectable moiety by being cleaved by an enzyme characteristic for the contaminants is a methylumbelliferyl derivative, wherein the detection step is performed by measuring fluorescence of the detectable moiety and wherein fluorescence is measured directly on the liquid vehicle without interruption.

Koumura *et al.* teaches a method wherein a liquid sample of viable microorganisms (bacteria, fungi, etc.) are contacted with methylumbelliferyl derivatives in a liquid vehicle that upon hydrolysis by enzymes characteristic to the microorganisms form fluorescent products which are measured directly in the liquid vehicle (Column 11, Claim 1).

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It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the chromogenic filtration method for the detection of viable microorganisms (bacteria) as taught by Tuompo *et al.* with the use of methylumbelliferyl derivative substrates and direct measurement method of Koumura *et al.* because the use of fluorescent vs. chromogenic substrates in the detection of microorganisms is well known in the art. Both references teach the detection of bacteria with substrates which are either chromogenic or fluorogenic and which upon interaction with characteristic enzymes form either a colored or fluorescent product. Therefore, one of ordinary skill in the art would conclude that either substrate would be suitable for detection of microorganisms.

The MPEP states:

The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)

Claims 1, 3, 4, 6, 7-11, 14, 15, 17, 20-25, 27, 28, 31-36, 39 and 48-51 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Laine *et al.* (US 6,090,573).

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Laine *et al.* teaches a method for detecting viable bacteria or fungi in liquid CSF samples, comprising: a) passing a known volume of diluted liquid medium through a closed, sterile filter from influent to effluent side in a filter device by positive pressure filtration thereby concentrating (retaining) the bacteria on the influent side of the filter device, b) contacting the influent side of the filter device with a liquid medium containing a chromogenic lysozyme-alkaline phosphatase or horseradish peroxidase conjugate detect reagent and an alkaline phosphatase or horseradish peroxidase substrate that though cleavage by bound enzymes produces a detectable moiety (color), and c) allowing the substrate to interact with the bacteria on the influent side of the filter for a period of time, detecting the detectable moiety by interrupting (eluting) contact between the substrate and detect reagent bound bacteria by evacuating the product from influent to effluent side of the filter and correlating the detection of the moiety to the presence of bacteria in the sample and comparing the data to standards (Column 45, Lines 58-67 and Column 46, Lines 1-30).

Laine *et al.* teaches that the method is applicable to biological samples including biological materials carried in the air or water (e.g. bacteria, fungi spores and the like) and collectable therefrom (Column 23, Lines 36-41).

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It is inherent in the method of Laine *et al.* that the liquid vehicle containing the chromogenic substrates comprises multiple substrates providing multiple signals that are combined into one measured signal value because the liquid vehicle contains multiple molecules of the chromogenic alkaline phosphatase or horseradish peroxidase substrate which combine to give a total, measurable color formation, and that the amount of substrate does not limit the rate of production of the detectable moiety. It is inherent that the detectable moiety would be detected in the liquid vehicle as some liquid vehicle would inevitable be retained in the filter along with the substrate and colored product. It is further inherent that the rate of production of the detectable moiety would be a function of the quantity of bacteria in the medium as it logically follows that more bacteria would equal more available enzyme for reaction with the substrate and result in a greater rate of production over a sample containing less bacteria. It is an inherent property of the closed, sterile filter device of Laine *et al.* would be disposable as nearly everything can be considered "disposable", giving the term its broadest, reasonable interpretation.

The teachings of Laine *et al.* were discussed above.

Laine *et al.* does not teach a method wherein the gaseous medium is air; wherein at least one substrate includes at least two substrates that produce detectable moieties providing distinguishable signals; wherein evacuation is obtained by applying elevated pressure on the influent side of the filter or applying a lowered pressure on the effluent side of the filter; wherein the filter has a pore size large enough to let the detectable moiety pass through the filter; wherein the correlation comprises the use of a pre-determined standard curve that expresses the relationship between the amount of microorganisms and the amount of the detectable moiety under standard conditions or wherein the detectable moiety is detectable in an amount of at most 100 picomoles, 50 picomoles, 20 picomoles, 10 picomoles or 1 picomole.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Laine *et al.* to detecting microorganisms in air by detecting picomolar amounts of detectable moiety cleaved by enzymes characteristic for contaminating microorganisms because the reference teaches that the method is suitable for the detection of airborne microorganisms collected from the air and because it is desirable to detect contaminating microorganisms using the least amount of detection material possible. Motivation to make this change would come from the teachings of the reference which teach the applicability of the method to detection of microorganisms from either air or liquid samples.

One of ordinary skill in the art would have recognized the advantageous property of detecting a contaminating microbe in the least amount possible, as obviously detecting a small amount of contamination is better than only detecting gross contamination. One of ordinary skill in the art at the time of the invention would have recognized that the result-effective adjustment of conventional working parameters (e.g., determining the least amount of detectable substrate released by microbial action) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. It would have been obvious to one of ordinary skill in the art at the time of the invention to select a pore size which was sufficient to retain the microorganisms being assayed. One of ordinary skill in the art would have recognized that a filter of sufficient pore size to retain a microorganism would still be too large to retain a chromogenic molecule in solution.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Laine *et al.* to utilize two substrates providing distinguishable signals because the reference teaches the detection method using two separate distinguishable signaling moieties and combination of the two substrates for the same purpose would flow naturally from the teachings.

The MPEP states:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose[T]he idea of combining them flows logically from their having been individually taught in the prior art."

In re Kerkhoven, 626 F.2d 846,850, 205 USPQ 1069, 1072 (CCPA 1980)

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It would have been obvious to one of ordinary skill in the art at the time of the invention to evacuate (elute) the colored enzymatic reaction product by applying either an elevated pressure on the influent side of the filter or applying a lowered pressure on the effluent side of the filter because one of ordinary skill in the art would have recognized this as an automation of the gravity filtration process and the automation of a previously manual activity is *prima facie* obvious (See MPEP, *In re Venner*). Further, the reference teaches the use of positive pressure as a means of filtration of the samples and thus the use of positive or negative pressure to facilitate the movement of materials would have been obvious to those of ordinary skill in the art at the time of the invention.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a pre-determined standard curve in order to correlate the resultant data from the method of Laine *et al.* by comparison of the two because the use of standards and standard curves would have been well known to and within the purview of, those of ordinary skill in the art at the time of the invention.

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The reference already teaches the comparison of data to standards and the further generation of a standard curves is routine in the art. One of ordinary skill in the art would have been motivated to make this modification because the use of standards and standard curves as a means of removing background or interfering data would improve the accuracy of the experimental data and because detecting miniscule amounts of fluorescent compounds are well known and routine to those of ordinary skill in the art.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL C. MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner
Art Unit 1657

07/21/09

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